The Baillie Lectures

ON

THE CARDIO-VASCULAR CHANGES OF RENAL DISEASE, WITH SOME OBSERVATIONS ON THE LARGER ARTERIES.

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LECTURE I.

Delivered on June 19th, 1895.

GENTLEMEN,—Excepting what has to do with bacteria it may be said that no observations in pathology have been so fruitful in results as the great discovery of Bright. I do not now propose to deal with this as regards the kidneys themselves, but only to touch upon some of the systemic consequences of renal disease which Bright partly, I may say in large part, made known. Bright noticed the hypertrophy of the left ventricle, and attributed the muscular increase to abnormal resistance. He inferred that there was an obstacle in the outward course of the blood, and assigned the capillaries as its probable situation. The immediate cause he considered to be in the impurity of the blood, which in some way interfered with its transit through these channels, which expose to the blood so large a surface and maintain with it such intimate relations. This theory held its ground without modification or question until Dr. (now Sir George) Johnson observed the thickening of the muscular coat of the arterioles, and was led to the belief that the hindrance was not in the capillaries, as Bright had supposed, but in the minute arteries thus thickened. Johnson argued that the capillaries were not muscular, and therefore not contractile, while the arterioles were both. In this view the arterioles became hypertrophied in their efforts to keep the impure blood out of the tissues; the heart became hypertrophied in its endeavours to overcome the resistance thus occasioned. The muscularity of the arterioles is not to be disputed, and it is known to physiologists that under certain influences, connected particularly with the nervous system, these vessels have the power of contracting, and so cutting off the blood from the tissues; but whether this stopcock action, as Johnson called it, is the essential factor in the cardio-vascular change of heart disease remains to be seen. The capillaries have been shown to be contractile, though not muscular, and the observations of Johnson do not disprove the theory of Bright.

Leaving this contest as yet undecided, I must note the appearance of another combatant, or rather hostile alliance, upon the field. Sir W. Gull and Dr. Sutton, neither of whom, I grieve to say, are with us now, came down in force upon the position of Johnson, and a great battle ensued, which was waged with obstinacy and even with asperity. The allies disputed the muscular thickening of the arterioles, and maintained that the only thickening was of the fibrous tissue. Johnson, in upholding the muscular increase, denied the fibrous, the appearance of which he held to be delusive and the result of reagents. The contest was the more obstinate because there was right on both sides, and the more embittered because on both sides there was wrong. Without staying to recall the fortunes of the fight, I may say that I took then, and have taken since, some pains to satisfy myself of the actual condition of the arterioles, and will briefly repeat, what I said at an early stage of this controversy, that the muscular thickening as described by Johnson is a fact which does not admit of doubt. On the other hand, it is equally certain that with this there is fibroid overgrowth, however brought about. The champions of fibrosis did not attribute the vascular change to the renal or acknowledge any steps in the pathological process, but they regarded both as the parallel and simultaneous results of a baneful tendency which pervaded the whole body like original sin, affected at the same time the vessels and the viscera, and produced a general deterioration, which they likened to the effects of age. This comprehensive theory is probably not entirely without foundation; there *is* such a thing as general fibrosis, particularly as a form of senile decay, and of this general fibrosis the granular kidney may sometimes be a part. But it is abundantly clear that this explanation suffices but for a small minority of the cases in which cardio-vascular changes are associated with renal. By far the greater number begin with disease local to the kidney, and proceed from step to step through the blood to the vessels and the heart. Inflammation limited to the kidney, produced by cold or scarlet fever, perhaps in a child where there can be no question of general fibrosis, except as a result of renal disease, is constantly and rapidly followed by the special cardio-vascular hypertrophy, and that in its most extreme and characteristic shape. That the granular kidney is essentially a local matter and not a mere subdivision of a general fibrosis, as Gull and Sutton tried to make us believe, is borne out by what happens to the liver. Of all the organs in the body the kidney and the liver are the most liable to fibrotic change. If the kidney is affected thus merely as part of a general change the liver surely ought to participate. But it does not do so. I found that in 250 cases of granular degeneration of the kidney, the liver displayed the corresponding change—that is, cirrhosis—in only 37 instances, a proportion of 1 in 7.[1] Granulation of the kidney and cirrhosis of the liver do not go together, as they should do if the fibrotic change in each were due to a common cause. The fact is that, putting aside the general effects of valvular disease of the heart, the liver and kidney are each influenced by causes proper to themselves, not common to the whole body. The liver is made fibrotic chiefly by alcohol, the kidney chiefly by climate, lead, gout, heredity, and as the sequel of acute nephritis. It has always seemed to me that the morbid independence of these organs is a strong if not a conclusive argument against the theory of general fibrosis as propounded by Gull and Sutton. On every ground, therefore, we must accept that as a *general rule*—I do not say there are no exceptions, but I am sure they are few—the renal change is the initial mischief, the *fons et origo* of which the cardio-vascular changes are the results.

The only question that presents itself as admitting of doubt is by what process the renal change brings about the cardio-vascular. The impurity of the blood due to the imperfect action of the kidneys may be accepted as an intermediary, but how does it produce the effects in question? There is presumably an obstruction which gives rise to increased blood pressure, and this to hypertrophy of both muscle and fibre. But where is the obstruction? Is it in the capillaries, as Bright supposed, or are we to place it with Johnson in the arterioles? It seems unlikely at first sight that the heart and the arteries should become hypertrophied by acting against each other—it looks like a want of the common consent which we usually find in nature; but how shall I say it is not so? There are many things which are too wonderful for us, four of which have been mentioned by a royal and inspired author. The action of the heart and vessels may be, like these, beyond our comprehension; but it is not beyond our inquiry. I have ever found, when a difficulty presented itself, that the best way was not to argue or even to reflect, but to seek for additional facts. Being able to get them is the great advantage we have over our brethren the theologians. The facts at their command cannot be added to by observation, whatever talent may be expended in reconsidering the stock in hand. With us the main endeavour is to collect fresh particulars, and nothing further is necessary than to let them speak for themselves. Unlike the students of theology, we are able to push our inquiries beyond death, and take for our motto, "Nec silet mors."

As possibly throwing light upon the rival theories of obstruction in the capillaries and in the arterioles, I thought it worth while to look more widely than had hitherto been done at the distribution of the arterial hypertrophy. If this should prove to be limited to the smaller vessels, which alone can be credited with the stopcock action, then the stopcock or inhibitive action may be the cause of the hypertrophy, or of as much of it as concerns the muscular coat; if, on the other hand, the large arteries should be found to partake of the same alteration, then we must look for some cause which acts alike on large and small. With this view I have examined a series of arteries, including some of the largest: the aorta, the innominate, the common femoral, and the renal. Sections of these vessels made carefully in the same respective

[1] Albuminuria, second edition, p. 171.

situations were placed under the microscope and outlined on paper with the camera lucida and a uniform magnifying power of 6·35 diameters. The tracings thus obtained were then measured both as to the thickness of the wall and the circumference of the vessel. The number of vessels thus treated amounted to 139, which were supplied by forty-nine individuals mostly chosen as the subjects of marked renal disease or as presenting the type of health. The conclusions are based upon the whole number of vessels of each kind and not derived from selected specimens. As a standard of health I have taken eighteen post mortems, generally after accident or acute disease—ten of males and eight of females. In the male series I have added two cases of acute nephritis, in which, as there was no time for, nor any evidence of, cardio-vascular change, the vessels may be taken as healthy and as furnishing a second standard of comparison. The granular kidney is represented by sixteen male subjects and seven female. In the latter series I have thrown together, as exhibiting virtually the same condition, and that the fibrotic, kidneys described as *granular* and as *white contracting*. The male series shows that with the granular kidney the aorta is thicker than in health as 42 to 39, and thicker than with acute nephritis as 42 to 31. The innominate with the granular kidney gives a thickness of 0·41 in., that with health 0·35 in., and that of acute nephritis 0·30 in. The common femoral gives with the granular kidney a thickness of 0·33 in., with health that of 0·26 in., and with acute nephritis that of 0·24 in. The renal gives with the granular kidney a thickness of 0·25 in. in health, and with acute nephritis one of 0·18 in. Both coats are thickened, as will be seen on reference to the accompanying table. The muscular shows the change with more exactness than the fibroid, for it is not exposed in removal, or liable, as the outer coat is, to have any part left behind. The circumference of the vessels of each kind is also increased with the granular condition, that of the aorta giving 13¾ in., as compared with 11¾ in. in health and 10¾ in with acute nephritis. The innominate, femoral, and renal showed similar increase under the same circumstances, as is displayed in the table. The comparison, as far as relates to the female sex, will be seen to give similiar evidence. The aorta, the innominate, and the femoral are all increased under the renal change in question in the total thickness of the wall, in the thickness of the muscular coat, and in circumference The only exception is in the case of the renal artery in the female, which presents an increase of circumference, but none in the thickness of the wall; only eight specimens, however, of this vessel in this sex were examined, and the number is too small to give weight to the exception.

I have added as collateral illustrations two instances which show the absence of arterial thickening, as of cardiac hypertrophy, with the large white and the lardaceous kidney; and a third which presents a large amount of aortic thickening in connexion with atheroma without renal disease. This aorta, which displayed a large endoarterial deposit, gave a total thickness of 0·57 in., which was greater than those in any of the renal cases, the thickest aorta with renal disease measuring 0·55 in. With the aorta thus thickened by atheroma the change did not extend to the innominate, which was thinner than the average of health.[2] The above measurements will, of course, be understood to apply not to the actual dimensions of the vessels but to those of the representations uniformly magnified as stated.

It has been well known since the observation of Sir G. Johnson—which represents a great truth, however it is to be interpreted—that with the chronic granular kidney the arterioles, even to the smallest, become hypertrophied. For the purpose of this inquiry I thought it would be of interest to ascertain as far as practicable how the degree and kind of thickening here compared with that of the larger vessels. To this end I have examined afresh a number of minute arteries belonging to the pia mater and median fissure of the brain, which are in my possession as the results of former work. Some have been preserved in Canada balsam, others in glycerine. I have dealt with these specimens graphically, making outlines of them with the camera lucida, as in the case of the larger vessels. I may say that I have made no selection—by judicious selection it is possible to prove anything—but I have taken all that came to hand as either typically healthy or connected with typical granular kidneys. The results are before you. The outlines show that under renal disease there is generally, but not universally, thickening of the wall, and that this affects both the muscular and the fibrous coats. The total thickening, and that of each coat, is, judging by the eye, generally greater in the small vessels than in the larger, though demonstrably present in both.

Putting all the facts together, and including what is common knowledge as to the left ventricle, we may formulate the general statement that in connexion with the chronic granular kidney we have hypertrophy of the muscle and of the fibrous tissue belonging to the whole arterial system connected with the left side of the heart, and of the muscle of the heart itself. It is probable that had the inquiry been carried into the pulmonary vessels similar changes might have been found there. We see indications of them in the hypertrophy of the right ventricle, which in these circumstances is almost invariably associated with that of the left, though on a smaller scale. Looking at the import of the changes which have been recorded, we recognise, first, the general application of the ancient dictum that muscle becomes hypertrophied when resistance is opposed to its contraction. We next see the influence of another law, which may act together with, or independently of, the first—namely, that tissues, whether epithelial, fibrous, or muscular, become over-nourished and overgrown as the result of habitual congestion or over-pressure, or undue retention, of blood within them. As

[2] I may introduce a word as to the methods employed. Sections of the arteries were cut with the microtome and mounted on slides for the microscope. These were reflected on paper with the camera lucida and carefully outlined, all with exactly the same microscopic and optical arrangements. With the magnifying power used the vessels were presented as large enough to be accurately measured. The thickness of the wall was ascertained with a rule graduated to hundredths of an inch. The circumference, taken along the outer edge of the muscular coat, was measured with a rotating instrument such as is used for estimating distances on maps. This gave the circumference in inches and fractions of an inch. The enlarged figures to which I have referred were displayed in the course of the lectures. I believe the measurements may be accepted as accurate.

THICKNESS AND CIRCUMFERENCE OF ARTERIES (MAGNIFIED 6·35 DIAMETER). (Mean Measurements in Inches.)

Male Adults.

State of kidney.	Number of cases observed.	Aorta.			Innominate.			Femoral.			Renal.		
		Total thickness.	Muscular thickness.	Circumference.	Total thickness.	Muscular thickness.	Circumference.	Total thickness.	Muscular thickness.	Circumference.	Total thickness.	Muscular thickness.	Circumference.
Healthy	10	0·39	0·29	11⅜	0·35	0·27	8⅝	0·26	0·13	4¼	0·18	0·10	3
Acute nephritis; no cardio-muscular changes	2	0·31	0·26	10¾	0·30	0·22	7¼	0·24	0·14	4⅓	0·18	0·08	4
Large white kidney	1	0·35	0·25	12	0·40	0·30	8	0·30	0·20	5	—	—	—
Granular	16	0·42	0·31	13¾	0·41	0·29	8¾	0·33	0·21	6¼	0·25	0·14	3½
Lardaceous kidney	1	0·30	0·27	12	—	—	—	0·35	0·25	5½	—	—	—
Highly atheromatous aorta	1	0·57	0·38	15½	0·30	0·23	6½	—	—	—	—	—	—
Female Adults.													
Healthy	8	0·34	0·26	11	0·26	0·24	7	0·24	0·15	4⅓	0·21	0·13	3
Granular or white contracting kidney	7	0·38	0·30	12½	0·36	0·27	9	0·29	0·16	5	0·19	0·11	3½

regards renal disease, it is impossible to separate the question of obstruction ahead from that of over-pressure by their contents upon the arterial walls. Some of the forms of renal disease are attended from their outset with increased blood pressure, others are not. When the pressure is increased, then, sooner or later, there is hypertrophy; when it is not increased there is none. This state of pressure or tension precedes the hypertrophy, for it is evident to the finger, the sphygmograph, and the stethoscope long before there has been time for any structural change. The granulating kidney and the lardaceous may be instructively contrasted. The granulating kidney — beginning, say, in nephritis—is attended from the very first with increased tension and followed as surely by hypertrophy. The lardaceous condition begins with no increase of tension or even with a lack of it; the heart remains small to the last, or, at least, until other renal changes are superadded. It is clear that there is a necessary connexion between the over-tension and the hypertrophy; and as the cause precedes the effect, it must be supposed either that the tension causes the hypertrophy or else that both are the results of some common cause. Searching for the immediate cause of the increase of tension and the hypertrophy which follows upon it, we can only attribute one and both to a difficulty in the emptying of the arterial system caused by an obstruction at or near its outlet, due to the morbid condition of the blood. So far all seems clear. The increased retention of blood within the arterial system is an adequate cause for vascular and cardiac thickening, on the principle which has been already adverted to, by which congestion causes hypertrophy. This would seem to be the essential and simple cause of the fibroid thickening. With regard to the muscular there are other considerations. The arteries are alternately filled by the ventricle and emptied by their own contractility. Peripheral resistance will oppose their contraction and thus occasion muscular hypertrophy. With the large arteries this rule seems of obvious application; they are in the same case as the heart and owe their hypertrophy to similar means. With regard to the minute and terminal arteries, other modes of action are to be taken into view. These vessels, which are known under certain circumstances to exert a special contractile power and thus cut off the blood from the capillaries, have been supposed to do this in renal disease and to owe their hypertrophy to their efforts not to accelerate, but to retard the current. I will not argue for this view or against it, but content myself with stating the facts, or what appear to me to be such, which bear upon it. I think it must be allowed that the smaller vessels are generally more thickened than the larger—at least, I have seen some examples of extravagant thickening among the smaller which I have failed to find in the larger vessels.

It often appears that the calibre of the small vessels is lessened in comparison with the thickness of the walls, whereas with the larger there is dilatation as well as parietal thickening. It looks as if the smaller vessels had some special cause of hypertrophy beyond that which affects the larger. There may be a special inhibitory mandate addressed to their muscular tissue, but against this we have to place the fact that the fibrous tissue, to which no such mandate could be held to apply, is at least equally thickened. Whatever be the cause of the hypertrophy, it must relate equally to both coats.

In searching for the primary seat of obstruction, however our attention may be arrested by the arterioles, we must not disregard the capillaries. These have been proved to be contractile, though they are not muscular.[3] These vessels are in more intimate relation to the blood than any others, and may be supposed to be the first to be influenced by its abnormal conditions; and as evidence that they are so influenced we have the appearance of dropsy—or, in other words, of abnormal capillary transudation—at the outset of renal disease. This process is capillary and not arterial, and at least points to a morbid condition of which the capillaries, not the arterioles, are the seat. Arterial obstruction, indeed, must be prohibitive of dropsy by cutting off the blood from the vessels which are its source. These considerations appear to indicate that, whatever be part of the terminal arteries, the capillary system is the point of departure of the series of changes which have been described. Whether these terminal arteries have any special sympathy with the capillaries with which they are so immediately connected is a question which suggests itself. Whatever be the explanation of the vascular changes upon which I have dwelt, it must include the fibrous thickening as well as the muscular.

Without attempting to pursue these questions to the end I will content myself for the present with having demonstrated the fact that under renal disease, putting aside the pulmonary department to which the same rule probably applies, there occurs a hypertrophy of the cardio-arterial system which is universal from its origin to its termination, and comprises not only the ventricle and the arterioles, but affects also the intermediate arteries of every size.

In conclusion, I have to thank Dr. Rolleston, Dr. Lee Dickinson, and Dr. Cyril Ogle for procuring the specimens of which I have made use. My especial thanks are due to Dr. Rolleston—and to a larger extent to Mr. Fenton—for cutting and mounting the sections.

[3] Paper by Dr. Roy and Dr. Graham Brown on "The Blood-pressure and its Variations in the Arterioles, Capillaries, and Smaller Veins." (Journal of Physiology, 1879-80, Part 2, p. 323.)

A Clinical Lecture

ON

CHRONIC INFLAMMATION OF THE UTERUS.

Delivered at the Middlesex Hospital on June 20th, 1895,

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GENTLEMEN,—The subject which I have chosen for this afternoon's lecture is probably the commonest disease to which a woman is liable, and it is not often that one or more of the beds in Prudhoe Ward are not occupied by a patient suffering from chronic inflammation of the uterus. Under the disease just mentioned I include inflammation affecting not only the parenchyma of the uterus (metritis), but also that involving the membrane lining the cervical canal (endocervicitis) and that lining the uterine cavity (endometritis). All the tissues of the uterus are more or less involved in chronic metritis, so that usually endometritis cannot clinically be dissociated from metritis, although in some cases the endometritis is predominant—in others the metritis. The microscopical appearances, thanks to Wyder, Ruge, and others, are now well known, and in briefly mentioning them I will follow the views of Wyder.

When the uterine wall is the chief seat of inflammation we find the whole uterus enlarged—perhaps even to the size of a man's fist—by hypertrophy of the connective tissue with usually some muscular hypertrophy also. The arteries and veins are much thickened by hypertrophy of the tunica adventitia. The connective tissue remains permanently hypertrophied and does not undergo cicatricial contraction. When the membrane lining the uterine cavity is chiefly affected the changes are such that they can be classified under the following heads: (*a*) chronic hæmorrhagic or villous endometritis, (*b*) chronic catarrhal or glandular endometritis, and (*c*) chronic interstitial endometritis.

In the villous or hæmorrhagic form the mucous membrane is greatly hypertrophied, perhaps to four or five times its usual thickness; it is deeper in colour and, instead of being smooth, has become fungoid, and the projections may form true polypi. In some cases there are found small transparent vesicles, which under the microscope are seen to be dilated glands, the openings of which are closed by connective tissue. The inter-glandular tissue is very vascular. In the glandular or catarrhal form the glands are enormously increased in size and become convoluted at their deep extremities; there is also an increase in their number, so that both hypertrophy and hyperplasia coexist, but otherwise the glandular tissue is normal in structure. In the interstitial form a new connective tissue is developed between the glands, and in some parts it converts the latter into cysts; in others of longer duration the glands may have disappeared altogether, so that the mucous membrane is represented by a layer of connective tissue lined by epithelium.

Causation.—It is becoming more and more a well-recognised fact that in the vast majority of cases of chronic inflammation of the uterus the origin is due to bacterial infection. This infection may be, and too often is, gonorrhœal in character,